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A NOVEL AND EFFICIENT ROUTE TO CHIRAL 2-SUBSTITUTED CARBOCYCLIC 5'-N-ETHYL-CARBOXAMIDO-ADENOSINE (C-NECA)

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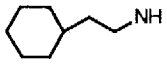
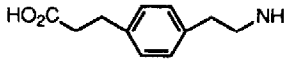
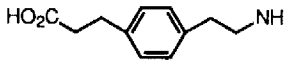
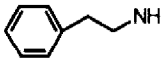
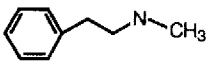
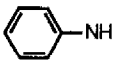
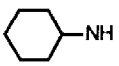
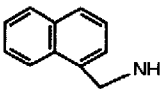
Summary: A series of chiral 2-substituted-carbocyclic-NECA analogs was prepared in seven steps with an efficient resolution. The overall yield is good and can be applied to the other carbocyclic nucleosides.

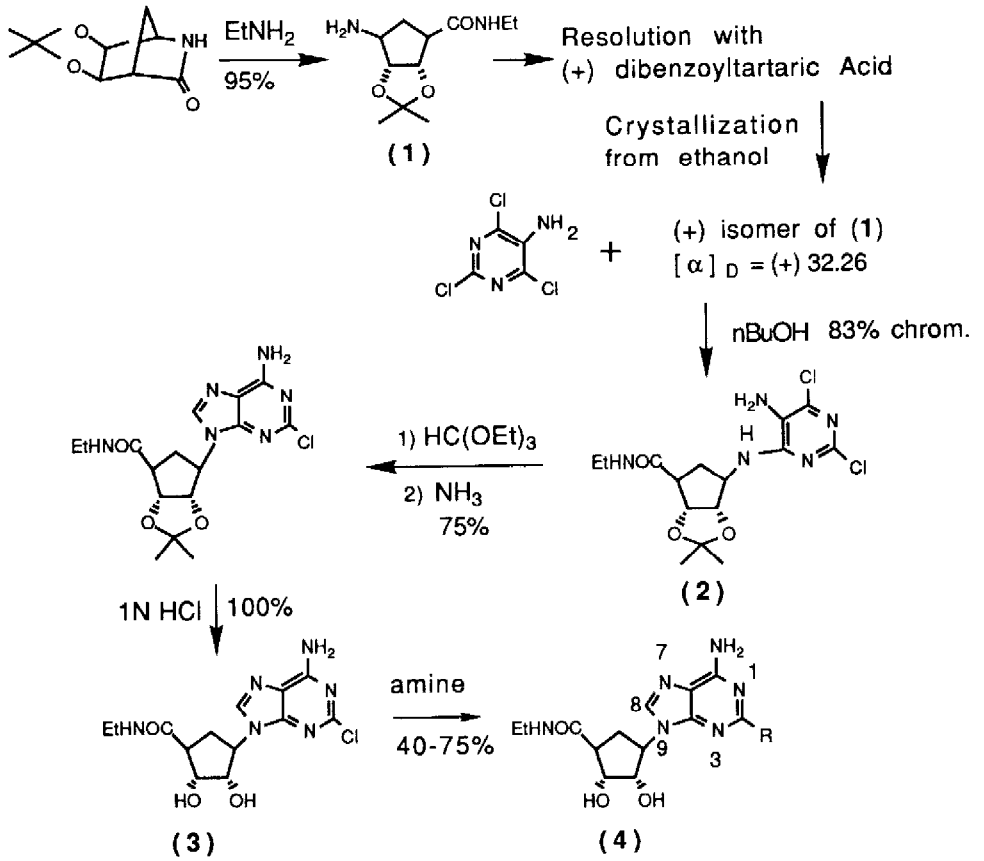
Adenosine is a potent coronary vasodilator, at first described by Drury and Szent-Gyorgyi in 1929[1].Since adenosine is short-lived in its action and orally inactive, many attempts have been made to develop orally active derivatives with higher potency and longer duration of action than the parent compound[2,3]. Recently, Daly[4] reported that 5'-N-ethylcarboxamidoadenosine (NECA) exhibits potent activity on the adenosine A_2 receptor , which is associated with vasodilation and hypotension in peripheral blood vessels[5]. Bruns et al[6] have also identified 2-(phenylamino) adenosine (CV1808) as an A_2 selective agonist which was developed by Takeda[7] Chemical Company as an antianginal agent. It is of interest to combine the N-ethylcarboxamide moiety at 5 position of the ribose portion and C2 substitution of the purine moiety into one molecule which may give more potent and A_2 selective compounds. Normal nucleosides are generally less stable to the action of nucleoside phosphorylases and hydrolases than carbocyclic nucleosides[8]. In view of these results, we were interested in the synthesis of 2-substituted carbocyclic NECA with the intention to develop a novel, more bioavailable drug as a potential therapeutic agent.

The synthesis started with 2-azabicyclo(2.2.1)heptyl-5,6-diol-3-one[9] which was protected with 2,2-dimethoxypropane to afford the acetonide as a white solid (m.p. 151-152° C) in quantitative yield. Lactam opening of the acetonide with neat ethylamine in a steel bomb at 140° C gave the amide **1** as an oil in 95% yield after chromatography. Resolution of amide **1** with dibenzoyltartaric acid by a single crystallization from ethanol resolved antipodes with rotations of (-) 31.15 (c 2.27, MeOH) and (+) 32.26 (c 1.52, MeOH) respectively. The optical purity of both isomers is greater than 95% according to NMR studies on the naproxen dervatives[11]. The absolute stereochemistry of the resolved amine was established by x-ray crystallography[12] . Reaction of the (+) amide **1** with 5-amino-2,4,6 trichloropyrimidine in refluxing n-butanol yielded **2** in 83% yield. The elaboration of the 9-adenyl substituent was accomplished by a known two step sequence[10]. Condensation of **2** with triethylorthoformate followed by aminolysis gave the corresponding protected C-NECA, which was then hydrolyzed with 1N HCl to give 2-chloro-C-NECA (**3**). Analagous to earlier work[13] ,reaction of **3** with various amines at 140° C resulted in moderate to good yields of 2-substituted -C- NECA derivatives (Table 1). We were pleased to see that the carbocyclic skeleton offers greater chemical stability than the corresponding ribose compounds. Both 2-chloro-adenosine and 2-chloro-NECA, which contain the glycosidic linkage, failed to afford the desired products when anilines were used. It is interesting to note that the chemical shift of the C8 hydrogen correlates well with the electronic donating effect of the C2 amine substituent (Table1).

Table 1

Compound	R	m.p. (°C) Recryst. Solvent	Chemical shift of C8 hydrogen (CD_3OD)	Rotation
3[a]	Cl	188-190 MeOH/Et_2O	9.27	-8.7[c] (c .8; MeOH)
4-1		>250 MeOH / Et_2O	7.90	-9.7 (c .3; DMSO)
4-2[a,b]		242-243 EtOH	8.08	-4.3 (c 1; DMSO)
4-3[a, b, e]		243-245 EtOH	8.11	+3.5 (c 1.1; DMSO)
4-4		243-245 MeOH / Et_2O	7.92	-2.9 (c .9; DMSO)
4-5[c]		194-197 MeOH / Et_2O	7.85	
4-6		268-270 MeOH / Et_2O	8.02	+1.5 (c 1; DMSO)
4-7[c]		228-229 MeOH / Et_2O	7.87	
4-8[c]		173-176 MeOH / Et_2O	7.89	
4-9[d]		210-213 °C MeOH / Et_2O	7.92	-31.6 (c .37; mixed solve)

a) This sample is the HCl salt. b) Sample was obtained after acidolysis of the corresponding t-butyl ester. c) Racemate was prepared from unresolved compound (1). d) Rotation obtained in a mixture of DMF : MeOH : 1N HCl (1:1:1). e) Sample was prepared from (-) isomer of (1).



The following is a typical procedure for the displacement of 2-chloro-C-NECA with amines to give compound **4**:

A combination of 2-chloro-C-NECA (1.5 mmol) and amine (5-10 mmol) was heated at 140^0 C under nitrogen atmosphere for 5h. The reaction mixture was then cooled to room temperature and triturated with ether. The insoluble material was collected and dried under vacuum. The solid obtained was triturated with water and the insoluble material collected and dried under vacuum to yield **4** (40-75%) as an off-white solid. The product can be either recrystallized or purified by reverse phase (C18) flash chromatography.

In conclusion, a novel and efficient route to chiral 2-substituted carbocyclic 5'-N-ethyl-carboxamidoadenosine was developed[14]. Those adenosine analogs show very good A_2 selectivity (A_1/A_2 = 5 ~ 400) with improved stability. Compound **4-2** is the most A_2 selective adenosine agonist reported (A_1 = 17 μM, A_2 = 43 nM). The detailed biological results will be published elsewhere.

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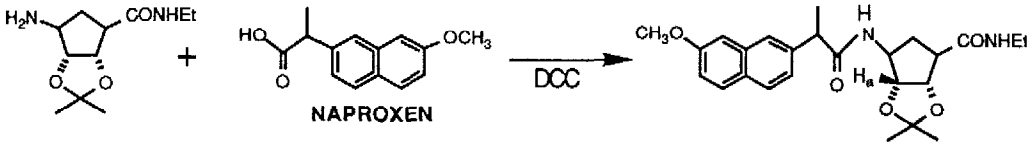
11 Optical purity is determined by the different chemical shift of Ha as shown below.



(-) AMINE Ha = 4.27 ppm
(+) AMINE Ha = 4.65 ppm

12 F. H. Clarke and J. Chen unpublished results.

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14 A similar route to the synthesis of chiral 2-substituted-aristeromycin was also developed and will be submitted as a separate paper.

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